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Management of Regional Metastases of Malignant Salivary Gland Neoplasms

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Abstract

Metastases from salivary gland carcinomas to the cervical lymph nodes are relatively uncommon. However, their impact on prognosis is significant and, thus, it is important to manage them appropriately. Treatment of clinically evident metastases consists primarily of surgery, frequently followed by radiation. Management of the N0 neck, on the other hand, remains controversial. While there seems to be agreement regarding the tumor and patient factors that make it more likely for a patient to harbor subclinical metastases in the lymph nodes, some clinicians prefer to treat those patients with surgery, i.e. a neck dissection, and others prefer to use elective radiation. These different approaches and their rationale will be discussed in detail.

Introduction

Metastasis to the cervical lymph nodes is relatively uncommon in carcinomas of the salivary glands; around 15% of parotid cancers and 8–10% of submandibular and sublingual tumors present with clinical evidence of nodal metastasis [1]. Although rare, tumor involvement of the lymph nodes has a major influence on prognosis. A significant difference has been noted between the survival rates of patients with cancer of the parotid with and without histologically proven lymph node metastasis of 70 versus 10%, respectively. The corresponding rates for patients with submandibular gland cancer are 41 and 9%, respectively [2, 3]. Similar differences in the 5- and 10-year overall survival rates have been reported more recently [4, 5]. Therefore, appropriate management of the regional lymph nodes is important in the treatment of patients with carcinoma of the major salivary glands.

The Clinically Positive Neck

Treatment of salivary gland cancer with clinically or radiologically obvious lymph node metastases consists of neck dissection (ND), followed in most cases by postoperative radiation. The type of ND is determined by the extent of nodal disease, with the purpose of the operation being the removal of all gross tumor present. For patients with parotid carcinomas who have a single involved node in level II, dissection of levels II-IV may be appropriate, while dissection of levels I-V may be necessary in patients with multiple palpable nodes in different levels of the neck. In patients with submandibular gland carcinoma who have undergone therapeutic ND, lymph node metastases have been found in all neck levels. Level I is the most frequently involved; however, high rates of lymph node metastases in levels IV (40%) and V (25%) have been reported [6]. Complete resection of the involved nodes can often be accomplished with preservation of the spinal accessory nerve, the sternocleidomastoid muscle, or the internal jugular vein.

The addition of postoperative radiation appears to be of value for patients with salivary gland cancer who have cervical lymph node metastases. While there are no prospective or randomized studies to support this use of postoperative radiation, the results of several retrospective reports have indicated that it improves local-regional control and survival [7–9]. Armstrong et al. [10] performed matched-pair analysis of patients treated for salivary cancer with nodal metastasis, with one cohort of patients receiving surgery alone and the other cohort receiving postoperative radiation. Each cohort included 46 patients matched according to age and tumor type, grade and stage. Treatment of stage III and IV cancers with postoperative radiotherapy resulted in better loco-regional control and survival compared with treatment with surgery alone. However, patients with low-grade or early-stage (I/II) disease did not appear to benefit from the addition of radiation. Terhaard [11] analyzed the roles of primary and postoperative radiotherapy in 538 patients treated for salivary gland cancer in the Netherlands. The tumor was located in the parotid gland in 59% of the patients, the submandibular gland in 14%, the oral cavity in 23%, and elsewhere in 5%. In 386 of 498 patients, surgery was combined with radiotherapy, with a median dose of 62 Gy. Postoperative radiotherapy significantly improved regional control in the clinically positive (N+) neck (86 vs. 62% for surgery alone). A more recent study of 50 patients with parotid gland cancer treated in the United Kingdom demonstrated excellent local control (96%) with surgery and postoperative radiotherapy [12].

The beneficial effect of postoperative radiation has also been suggested in studies of patients with submandibular gland and minor salivary gland cancers [13–16]. It is unclear, however, whether radiation should be prescribed to every patient with histologically positive nodes [17] or only to those with multiple positive nodes or extranodal tumor extension [18].

Although the results of recent studies of the use of combined therapy for treatment of the N+ neck in salivary gland cancers look promising, they still leave a lot to be desired [10, 17]. In analysis of malignant tumors of major salivary gland origin, Armstrong et al. found a 5-year local-regional control rate of 69% for a group of 23 patients with lymph node metastases who received radiation to the neck and of 40% for a group of 16 patients treated with surgery alone ($p = 0.05$). The corresponding survival rates were 49 and 19%, respectively ($p = 0.015$). More recently, a single institution report has suggested that combining radiation with platinum-based chemotherapy may improve long-term survival among patients with locally advanced salivary gland carcinoma [19]. Thus, this treatment approach warrants investigation in patients with salivary gland carcinoma and clinically obvious lymph node metastases.

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The Clinically Negative Neck

There is no general agreement to date about the management of the clinically negative (N0) neck in patients with cancer of the major salivary glands. The different management strategies that have been recommended over the years are outlined in table 1.

In a paper published in 1967 reporting a study that included 111 patients with malignant tumors of the parotid gland treated at MD Anderson Cancer Center, Bardwil [20] stated that elective ND had not been performed during the last 5 years of the study because he had found occult metastases in only 1 of 34 (2.9%) patients who had undergone this operation. Interestingly, however, he advocated 'careful dissection of the first echelon of lymph nodes for all lesions,' claiming that this adds little or no morbidity to the operation and if the tumor proves to be malignant, the procedure is generally adequate. For the next 2 decades, the surgeons at MD Anderson subscribed to this approach to the N0 neck in patients with salivary gland tumors [18, 21]. Then, in 1993, Frankenthaler et al. [22] reported the results of multivariate analysis of 11 clinical and histopathologic variables in patients who had undergone elective node dissection for cancer of the parotid gland. The factors that were correlated with the presence of occult cervical lymph node metastases were facial paralysis, an older age (>54 years), a high tumor grade, perilymphatic invasion, and extraparotid tumor extension. Interestingly, with the exception of older age, these factors were also associated with increased local recurrence and thus dictate the need for postoperative radiation, regardless of the presence or absence of occult metastases in the regional lymph nodes [23]. Another interesting finding of this study was that occult metastases were discovered by elective dissection of the lymph nodes in only 3% of the patients with low-grade tumors. Although staging ND may be helpful for determining the need for postoperative radiation in this group of patients, the operation would be unnecessary in 97% of the cases. In 1980, Johns [24] carried out a review of the literature and of the experience of the University of Virginia with the treatment of parotid tumors. He advocated treating the neck on the basis of the stage and histology of the primary tumor and felt that ND was indicated in patients with tumors of stages T3 and T4; for T1 through T2 tumors of high-grade histology, he advocated dissection of the first echelon of lymph nodes [24]. In 1989, Spiro et al. [25] published a review of 44 years of experience at the Memorial Sloan-Kettering Cancer Center. This group stated that elective ND may be beneficial in patients with anaplastic or squamous carcinoma because 58% or more of them will develop cervical metastases. Staging supraomohyoid ND was thought to be appropriate for patients with other types of high-grade tumors [25]. A few years later, similar recommendations were made by Califano et al. [26] from the University of Naples. A later study from Memorial Sloan-Kettering suggested that in patients with small, low-grade tumors that are adequately excised, elective treatment of the neck is not necessary [23]. On the other hand, this treatment is warranted in patients whose tumors are larger than 4 cm or are high grade and in whom the risk of occult lymph node metastases is high [24]. In yet a different review of the same patient population, Armstrong et al. [1] advanced the notion that in the high-risk group, the N0 neck could be treated with either elective ND (incorporating at least levels I, II, and III) or 'elective postoperative neck irradiation.' They suggested that it may be reasonable to treat the neck electively with radiation for patients for whom postoperative radiation therapy is indicated according to the characteristics of the primary tumor. Their recommendation is based on the extensive experience reported, which indicates that either radiation therapy to the neck or ND can control clinically occult cervical metastases in epidermoid carcinoma of the head and neck.

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Table 1. The N0 neck in salivary gland cancer: management strategies over time

Bardwill [20], 1967	No elective radical neck dissection Dissection of first echelon nodes for all tumors
Johns [24], 1980	T1–T2: No neck dissection T3–T4: Neck dissection and radiation
Byers [21], 1982	Dissection of first echelon nodes in all tumors
Spiro et al. [25], 1989	Elective neck dissection for anaplastic or squamous carcinoma Staging supraomohyoid neck dissection for other high-grade tumors
Armstrong et al. [1], 1992	Elective neck dissection or elective postoperative neck irradiation for 'high-risk' tumors
Califano et al. [26], 1993	Neck dissection in cases of mucoepidermoid, anaplastic, and squamous cell carcinomas
Ball et al. [41], 1995	Neck dissection: high-grade tumors with positive jugulodigastric node biopsy (intraoperative frozen section)
Frankenthaler et al. [22], 1993	No elective neck dissection Elective postoperative neck irradiation for high-risk tumors
Kelley and Spiro [17], 1996	Elective treatment of the neck for tumors larger than 4 cm or high-grade tumors
Medina [33], 1998	Intraoperative assessment of level II nodes If suspicious and frozen section examination reveals metastases: ND Otherwise, elective postoperative neck irradiation if the primary tumor exhibits high-risk clinical-pathological characteristics
Wang et al. [42], 2012	Comprehensive ND and postoperative radiation: high-risk tumors with adverse features Upper ND; postoperative radiation: moderate-risk tumors, depending on adverse factors and pN status Observation: low-risk tumors without adverse features
Herman et al. [27], 2013	T3–T4: Elective neck irradiation if postoperative radiation is indicated preoperatively (based on primary tumor characteristics)
Norbis et al. [28], 2014	Elective neck dissection for all patients

As shown in table 1, the debate continues to date, with some clinical studies suggesting that the appropriate treatment of the N0 neck is either ND or postoperative neck irradiation in select cases [27] and others suggesting that elective ND should be performed in all cases [28].

An important consideration in selective approaches to management of the N0 neck is the definition of a 'high-risk' tumor with regard to the risk of occult metastases in the lymph nodes. Today, it is generally accepted that the tumor histology, T stage and tumor grade are the most consistent predictors of the presence of nodal metastases. The risk of metastases is approximately 50% or higher when the tumor histology is undifferentiated carcinoma, adenocarcinoma, salivary duct carcinoma or squamous cell carcinoma. The risk is similarly high for high-grade mucoepidermoid carcinoma, unlike low-grade mucoepidermoid carcinoma and acinic cell car-

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Table 2. Variables correlated with the presence of lymph node metastases in cancers of the major salivary glands

1	High-grade tumors
2	T3 (?) and T4 tumors
3	Facial paralysis
4	Older age (>54 years [22], >70 years [43])
5	Extraparotid extension [42]
6	Lymphovascular invasion
7	Facial paralysis and perineural invasion [22, 33]

cinoma, for which the risk is 2–4% [1, 22, 29]. The reported prevalence of lymph node metastases also varies according to the disease stage, ranging from 16 to 33% for T3 tumors and from 24 to 50% for T4 tumors [1, 8, 26]. Beppu et al. [30] found that the incidence of lymph node metastases in patients with submandibular gland carcinoma ranged from 0% in T1 tumors to 33.3% in T2, 57.1% in T3 and 100% in T4 tumors. Other factors that have been reported to be correlated with the presence of lymph node metastases in salivary gland tumors are listed in table 2.

It is interesting to note that the currently accepted indications for prescribing postoperative radiation in patients with carcinoma of the salivary gland also include high risk and high-grade histology, stages T3 and T4, extraparotid extension, perineural invasion, a deep lobe location, close or positive margins and the presence of lymph node metastases [31–33].

Consequently, Medina [33] reasoned, along the lines suggested by Armstrong et al. [1], that since the characteristics of salivary gland carcinomas that dictate the need for elective treatment of the regional lymph nodes are, in essence, the same characteristics that dictate the need for postoperative radiation to the primary lesion, then it seems reasonable to treat the neck with elective irradiation in patients whose tumors exhibit these characteristics after adequate surgery of the primary tumor. Although this approach to the N0 neck seems logical, it has been criticized because it has not been tested prospectively, and it is assumed that elective neck irradiation is efficacious in the control of occult lymph node metastases from salivary gland carcinomas. Interestingly, two recent studies, albeit retrospective, have lent support to this approach. Chen et al. [31] studied 251 patients with carcinoma of the salivary glands and a clinically N0 neck who were treated with surgery and postoperative radiation therapy and who had not undergone previous ND. Postoperative elective neck irradiation reduced the 10-year nodal failure rate from 26 to 0% ($p = 0.0001$). The highest crude rates of nodal relapse among patients treated without elective neck irradiation were observed in those with squamous cell carcinoma (67%), undifferentiated carcinoma (50%), adenocarcinoma (34%), and mucoepidermoid carcinoma (29%). There were no nodal failures observed among patients with adenoid cystic or acinic cell carcinoma. These authors concluded that elective postoperative irradiation effectively prevents nodal relapses and should be used for select patients at high risk of regional failure. The second study was conducted by Herman et al. [27] to determine whether patients with high-grade salivary gland carcinoma and a clinically node-negative neck benefit from elective ND performed prior to postoperative radiotherapy. They studied 59 previously untreated patients with high-grade salivary gland carcinoma and an N0 neck who were treated with curative intent using elective ND ($n = 41$) or elective neck irradiation ($n = 18$). These patients underwent resection of the primary tumor followed by postoperative radiation. During a median follow-up period of 5.2 years (range, 0.3–34 years), there were 4 recurrences (10%) in the ND group and 0 in the neck irradiation group. They concluded that patients with high-grade salivary gland carcinoma and a clinically N0 neck who have undergone surgery and postoperative radiation are not likely to benefit from ND [27].

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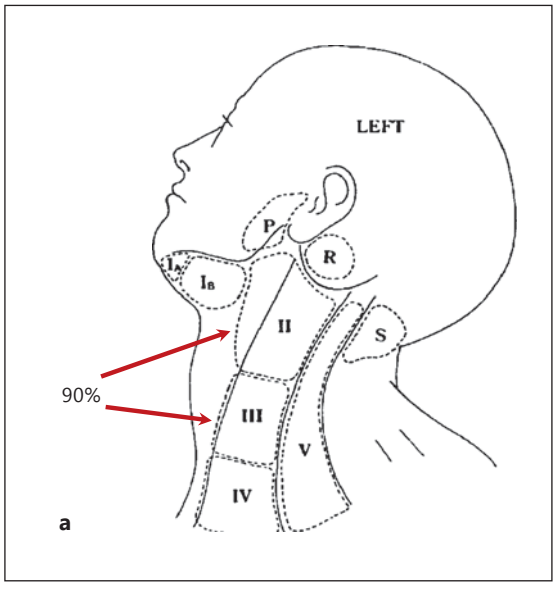


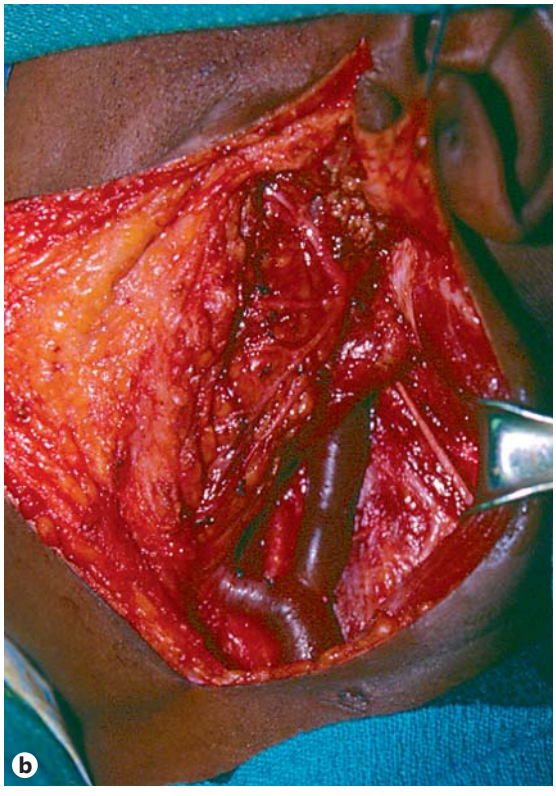
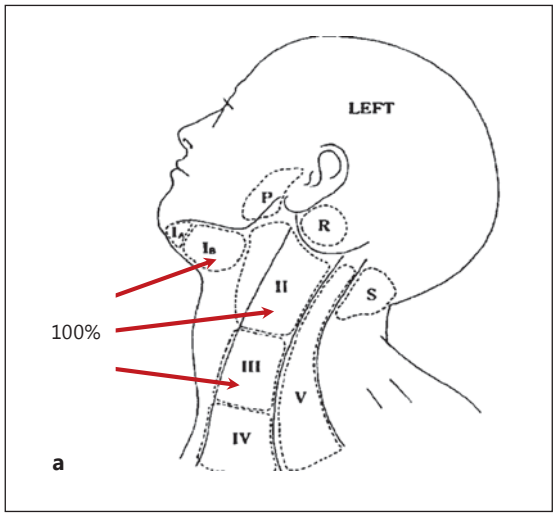


Fig. 1. a Distribution of occult lymph node metastases in parotid cancers. **b** Intraoperative photograph of parotidectomy and selective neck dissection of levels II and III.



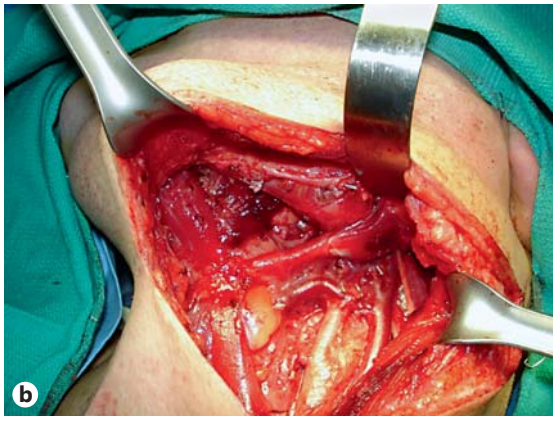


Fig. 2. a Distribution of occult lymph node metastases in carcinomas of the submandibular gland in levels II and III. **b** Intraoperative photograph of selective neck dissection of levels I (submandibular triangle), II and III.

Sentinel Node Biopsy in Primary Parotid Cancer

The incidence of occult metastasis in elective neck dissection (END) specimens has been reported to be between 20 and 37% [34, 35]. Thus, the performing of END for all cN0 parotid cancers implies that more than half of patients are over-treated. Sentinel node biopsy (SNB) is a

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technique used to select patients with occult metastases who would benefit from ND. The sentinel lymph node is the first node (in many cases, there are several sentinel nodes) to receive drainage from the primary tumor site. It is therefore the initial possible recipient of metastatic tumor cells and may be predictive of the histopathologic status of the remaining lymphatic neck area [36]. The SNB concept was introduced for nodal evaluation of head and neck squamous cell carcinomas localized to the oral cavity and oropharynx. It was determined to be a valid procedure for avoiding END and its potential morbidity [36]. As for primary parotid carcinoma, experience with SNB is very limited, although one of the first such reported experiences involved patients treated for parotid carcinoma [37]. Gould et al. [37] observed the so-called angular node in 28 parotid carcinomas; they based the decision on whether to perform ND on the results of frozen section analysis of this node. Thereafter, several authors suggested 'dissection of the first echelon of lymph nodes' [20, 24] or 'jugulodigastric node biopsy' with intraoperative frozen section analysis [33].

Approximately 80% of parotid carcinomas arise in the superficial lobe. In many of these cases, the first echelon is represented by the intraparotid lymph nodes. The mean numbers of intraparotid lymph nodes that have been reported are 7 (range, 3–19) in the superficial lobe and 2 (range, 0–9) in the deep lobe [38]. Furthermore, a statistically significant correlation ($p = 0.005$) has been observed between the presence of intraparotid metastatic nodes and neck node metastases [39]. Unfortunately, the lymphoscintigraphic identification of intraparotid nod metastases is challenging in many cases. The nodes can be easily missed due to close proximity to the primary tumor and injection site.

In 2006, Starek et al. [40] reported a study of 6 patients who underwent SNB; in all cases, selective neck dissection level II–V was performed. Two patients had true-positive results for the sentinel node, and there was one false-negative result that was interpreted as 'distortion of the lymphatic outflow resulting from intraparotid localization of lymphatic metastases'.

There are several documented reasons why there is no experience with performing SNB for parotid carcinoma: the lymphoscintigraphic identification of intraparotid lymph nodes may be difficult in many cases; intraparotid lymph nodes can be examined by frozen section analysis of a parotidectomy specimen; and lymphadenectomy of suspected nodes in level II for frozen sections or even END of level II or level III can easily be incorporated into the surgical approach with minimal morbidity and only a slight increase in operative time.

Conclusion

Regardless of whether a clinician chooses to treat an N0 neck with elective ND or elective postoperative radiation, only the ipsilateral side of the neck should be treated. The occurrence of contralateral lymph node metastases in tumors of the major salivary gland is negligible [17].

If a clinician elects to treat an N0 neck with ND, the type of ND should be tailored according to the distribution of occult metastases in patients with salivary gland carcinoma. The distribution of lymph node metastases in parotid carcinoma has been studied by Armstrong et al. [1]. Beppu et al. [30] noted that pathological neck lymph node metastases were found in levels II and III only in 27 patients with submandibular gland carcinoma staged as N0. Others have reported similar findings [6] (fig. 1, 2).

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